ORIGINAL ARTICLE

Efficacy of a Low-Cost, Heat-Stable Oral Rotavirus Vaccine in Niger

Sheila Isanaka, Sc.D., Ousmane Guindo, M.D., Celine Langendorf, Pharm.D., M.P.H., Amadou Matar Seck, M.D., Brian D. Plikaytis, M.Sc., Nathan Sayinzoga-Makombe, M.P.H., Monica M. McNeal, M.Sc., Nicole Meyer, M.Sc., Eric Adehossi, M.D., Ali Djibo, M.D., Bruno Jochum, M.S., and Rebecca F. Grais, Ph.D.

ABSTRACT

BACKGROUND

Each year, rotavirus gastroenteritis is responsible for about 37% of deaths from diarrhea among children younger than 5 years of age worldwide, with a disproportionate effect in sub-Saharan Africa.

METHODS

We conducted a randomized, placebo-controlled trial in Niger to evaluate the efficacy of a live, oral bovine rotavirus pentavalent vaccine (BRV-PV, Serum Institute of India) to prevent severe rotavirus gastroenteritis. Healthy infants received three doses of the vaccine or placebo at 6, 10, and 14 weeks of age. Episodes of gastroenteritis were assessed through active and passive surveillance and were graded on the basis of the score on the Vesikari scale (which ranges from 0 to 20, with higher scores indicating more severe disease). The primary end point was the efficacy of three doses of vaccine as compared with placebo against a first episode of laboratory-confirmed severe rotavirus gastroenteritis (Vesikari score, ≥11) beginning 28 days after dose 3.

RESULTS

Among the 3508 infants who were included in the per-protocol efficacy analysis, there were 31 cases of severe rotavirus gastroenteritis in the vaccine group and 87 cases in the placebo group (2.14 and 6.44 cases per 100 person-years, respectively), for a vaccine efficacy of 66.7% (95% confidence interval [CI], 49.9 to 77.9). Similar efficacy was seen in the intention-to-treat analyses, which showed a vaccine efficacy of 69.1% (95% CI, 55.0 to 78.7). There was no significant between-group difference in the risk of adverse events, which were reported in 68.7% of the infants in the vaccine group and in 67.2% of those in the placebo group, or in the risk of serious adverse events (in 8.3% in the vaccine group and in 9.1% in the placebo group); there were 27 deaths in the vaccine group and 22 in the placebo group. None of the infants had confirmed intussusception.

CONCLUSIONS

Three doses of BRV-PV, an oral rotavirus vaccine, had an efficacy of 66.7% against severe rotavirus gastroenteritis among infants in Niger. (Funded by Médecins sans Frontières Operational Center and the Kavli Foundation; ClinicalTrials.gov number, NCT02145000.)

From the Department of Research, Epicentre, Paris (S.I., C.L., R.F.G.); the Departments of Nutrition and Global Health and Population, Harvard T.H. Chan School of Public Health, Boston (S.I.); Epicentre (O.G., A.M.S., N.S.-M.), National Hospital (E.A.), and University of Niamey (A.D.), Niamey, Niger; BioStat Consulting, Jasper, GA (B.D.P.); Laboratory of Specialized Clinical Studies, Cincinnati Children's Hospital Medical Center, Cincinnati (M.M.M., N.M.); and Médecins sans Frontières Operational Center, Geneva (B.J.). Address reprint requests to Dr. Grais at 8 rue Saint Sabin, 75011 Paris, France, or at rebecca.grais@epicentre.msf.org.

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Rotavirus is a leading cause of severe gastroenteritis among young children and is responsible for approximately 37% of deaths from diarrhea among children younger than 5 years of age worldwide.[1,2] Two live, oral, attenuated rotavirus vaccines (Rotarix, GlaxoSmithKline, and RotaTeq, Merck) have met the prequalification requirements of the World Health Organization (WHO), stipulations that allow for purchase by United Nations agencies.[3] The efficacy of these vaccines has been shown, with an important effect on hospital admissions and mortality.[4-14]

Sub-Saharan Africa has the highest rate of death associated with rotavirus disease,[1] but vaccination on a large scale presents challenges.[15-17] Current prices of the two licensed vaccines are probably unsustainable without external subsidies. In addition, the global supply of the vaccines is constrained,[18-20] and unreliable transportation and storage systems make delivery of vaccines that require refrigeration difficult. A heat-stable, live, oral bovine rotavirus pentavalent vaccine (BRV-PV, Serum Institute of India)[21] was developed for sale at or below the current price of the two WHO prequalified vaccines that are supported by the Gavi Alliance (formerly the Global Alliance for Vaccines and Immunization). The introduction of BRV-PV may help to minimize the burden on already strained immunization programs. As part of an effort to identify rotavirus vaccines for use in resource-constrained settings, we assessed the efficacy and safety of BRV-PV against severe rotavirus gastroenteritis among healthy infants in Niger.

Methods

Study Design and Participants

We conducted a double-blind, placebo-controlled, randomized, phase 3, event-driven trial in Madarounfa, Niger, to assess the efficacy and safety of BRV-PV against severe rotavirus gastroenteritis. A placebo-controlled design was chosen because the vaccine was not licensed or available in Niger at the time of study initiation, and data were needed to inform policy decisions in low-resource countries.[22,23] After a parent or guardian provided written informed consent, healthy infants were randomly assigned in a 1:1 ratio to receive three doses of the vaccine or placebo at 6, 10, and 14 weeks of age. Since rotavirus circulates year-round in Niger,[24] enrollment was continuous beginning in August 2014. Infants were eligible if they were healthy and the parents resided in villages within the catchment area of study sites and intended to remain in the area for at least 2 years. Full details of the study design are provided in the protocol, available with full text of this article at NEJM.org.

The trial was conducted in accordance with Good Clinical Practice guidelines. The trial protocol was approved by the ethics committee of the WHO in Switzerland; the Western Institutional Review Board in Olympia, Washington; Comité Consultatif National d'Ethique in Niger; Comité de Protection des Personnes in France; and Hôpitaux Universitaires de Génève in Switzerland. A data and safety monitoring board regularly reviewed the trial data, and an independent adjudication committee reviewed suspected cases of intussusception. The first and last authors vouch for the completeness and accuracy of the data and all analyses and for the fidelity of the trial to the protocol.

Vaccine

The trial vaccine, the calcium carbonate buffer, and the placebo were developed and manufactured by Serum Institute of India, which donated the vaccine, buffer, and placebo. BRV-PV is a bovine–human reassortant vaccine containing rotavirus serotypes G1, G2, G3, G4, and G9 (>5.6 $\log_{10}$ fluorescent focus units per serotype per dose) and is stable for 2 years at a temperature of 37°C and for 6 months at 40°C.[21] The placebo was the same formulation but without the viral antigens. The vaccine and placebo were administered orally in liquid form and were identical in appearance and packaging.

The vaccine and placebo were stored at 2°C to 8°C from the time of shipping to arrival at the Epicentre facility in Maradi, Niger. There the vaccine and placebo were stored at temperatures not exceeding 25°C and, after dispatch, at ambient temperature until administration.

Study physicians at health centers administered the initial dose to infants who were 6 to 8 weeks of age, with each subsequent dose given at 4-week intervals (range, 3 to 8 weeks). Vaccination was delayed only if the child was unable to swallow, had a history of vomiting within the previous 24 hours, or required immediate hospitalization. Vaccines that were routinely adminis-

tered according to the guidelines of the Expanded Program on Immunization were concomitantly administered with the vaccine or placebo. No specific instructions to the mothers about breastfeeding were given at the time of administration.

RANDOMIZATION

Unique assignment numbers were prepared with the use of a computer-generated random-number list with nondisclosed permuted blocks of random sizes (DiagnoSearch Life Sciences). Vaccine and placebo packages were labeled with assignment numbers with identical presentation. All the practitioners and participants were unaware of the treatment assignments.

ASSESSMENT OF EFFICACY

We defined gastroenteritis as three or more looser-than-normal stools during a 24-hour period with or without vomiting. We used the 20-point Vesikari clinical scoring system to define severity,[25] with a score of 11 or more classified as severe; in post hoc analyses, a score of 15 or more was classified as very severe. Gastroenteritis episodes were classified as two episodes if they were separated by at least 5 consecutive diarrhea-free days.

Cases of gastroenteritis were captured through facility- and home-based surveillance on the basis of available evidence regarding health care–seeking behavior.[26] Trial staff members were assigned to all health facilities in the trial area (e.g., 1 hospital, 5 health centers, and 12 community health posts). Caregivers were informed about the signs and symptoms of gastroenteritis and were asked to seek care at a local facility free of charge. Home-based surveillance was used to identify episodes of gastroenteritis for which a caregiver chose not to bring the infant to a health facility. Caregivers were advised to immediately inform the trial's community health agent in their village if an infant had three or more looser-than-normal stools within a 24-hour period. Episodes that were not immediately reported to a health facility or to the health agent were captured during scheduled weekly home visits with the health agent. In such cases, daily home visits were conducted until resolution was confirmed with at least 5 consecutive diarrhea-free days.

Stool samples were collected for all episodes of gastroenteritis up to 7 days after the last day of symptoms. Such specimens, which were masked with respect to randomized group, were transported in freezer packs at 2°C to 8°C on the same day and frozen at −80°C for up to 5 days before testing. Rotavirus antigen in stool was detected by means of enzyme immunoassay (Premier Rotaclone, Meridian Bioscience), which was performed in duplicate, at the Epicentre laboratory located in the regional hospital in Maradi. A gastroenteritis episode was considered to be caused by rotavirus if any rotavirus strain was detected on enzyme immunoassay.

ASSESSMENT OF SAFETY

Adverse events included all untoward medical events and were assessed from the time of the first dose until 28 days after the third dose. Serious adverse events, including intussusception, were defined as any new health-related problem that resulted in death, was life-threatening, necessitated hospitalization or prolongation of existing hospitalization, or resulted in disability or incapacity; serious adverse events were to be assessed from the time of the administration of the first dose until the child reached 2 years of age. All adverse events and serious adverse events were assessed on the basis of facility- and home-based surveillance. Caregivers were informed of the signs and symptoms of adverse events and serious adverse events, including intussusception, and were asked to seek care at a local health facility or with the trial's community health agent when any event was suspected and of concern. Events that were not reported to a health facility or community health agent were captured during scheduled weekly home visits. In such cases, a symptom history was recorded through caregiver interview at the time of identification and during daily home visits until resolution.

END POINTS

The primary end point was the efficacy of three doses of BRV-PV versus placebo against a first episode of laboratory-confirmed severe rotavirus gastroenteritis. Secondary end points included analyses of vaccine efficacy against rotavirus gastroenteritis of any severity, against very severe rotavirus gastroenteritis, and against gastroenteritis of any cause. Other secondary end points were the incidence of immediate adverse events within 30 minutes after the administration of

any dose, adverse events that occurred after the first dose until 28 days after the third dose, and serious adverse events, including intussusception, hospitalization, and death.

STATISTICAL ANALYSIS

We determined that a sample size of 7700 infants would provide a power of a least 90% to detect a 50% true vaccine efficacy with a lower boundary of the 95% confidence interval of more than 0, assuming a 2% rate of severe rotavirus gastroenteritis and a 20% rate of nonassessibility (i.e., unavailable stool sample or laboratory result) among participants. Under these assumptions, 117 cases of severe rotavirus gastroenteritis (39 in the vaccine group and 78 in the placebo group) were required to establish 50% true vaccine efficacy. Since the trial was event-driven, we determined that data collection for the primary efficacy analysis would be cut off when we had identified 117 cases of severe rotavirus gastroenteritis that had occurred at least 28 days after the third dose of vaccine, which established November 26, 2015, as the cutoff date. The analyses that are presented here include follow-up to this date, although trial follow-up will continue for secondary end points and safety until the participants are 2 years of age.

Vaccine efficacy was calculated as the person-time incidence rate in the vaccinated group divided by the person-time incidence rate in the placebo group, multiplied by 100. The incidence rate was calculated as the number of infants who had at least one event divided by all available follow-up time (calculated as the total time until the occurrence of the event, the date of loss to follow-up, or data cutoff) with corresponding 95% confidence intervals derived from the exact confidence interval with the use of Poisson distribution. A participant was considered to be lost to follow-up after there had been no contact for 3 months after the last scheduled visit.

The per-protocol population, which was determined before unblinding, was considered to be the primary analysis population for vaccine efficacy. This population included infants who had received three doses of vaccine or placebo (complete course) without a major protocol violation and excluded those who had a laboratory-confirmed rotavirus episode between the time of the first dose of vaccine to 28 days after the third dose. Follow-up in the per-protocol population began 28 days after the third dose of vaccine. For the infants who had more than one episode of severe rotavirus gastroenteritis, only the first episode was counted toward the primary end point. Secondary analyses were performed in the intention-to-treat population, which included all the participants who had received at least one dose of vaccine or placebo, with follow-up beginning at the time of the first dose.

Safety analyses were performed in the intention-to-treat population and included follow-up from the time of enrollment until 28 days after the third dose (for adverse events) or until the end of follow-up (for serious adverse events). We used Fisher's exact test to analyze the between-group difference in the incidence of at least one adverse event and at least one serious adverse event.

We used the Kaplan–Meier method and the log-rank test to compare the rate of survival without an episode of severe rotavirus gastroenteritis during follow-up. We calculated the number of events that were prevented per 100 infants per year as 100 times the difference in the incidence rate of the placebo and vaccine groups; we derived the associated confidence interval using the method of Zou and Donner.[27]

All P values are two-sided, with a value of less than 0.05 considered to indicate statistical significance. No adjustment for multiple comparisons was made, since the single primary end point was the efficacy of three doses of vaccine against a first episode of severe rotavirus gastroenteritis beginning 28 days after the third dose. Missing data were considered to be missing at random, and no imputation was applied. All analyses were performed with the use of SAS software, version 9.3 (SAS Institute).

RESULTS

TRIAL PARTICIPANTS

From August 2014 through November 2015, we screened 4137 infants for participation in the trial. Of these infants, 4092 underwent randomization, received at least one dose of vaccine or placebo, and were included in the intention-to-treat population (Fig. 1). A total of 3508 infants (1780 in the vaccine group and 1728 in the pla-

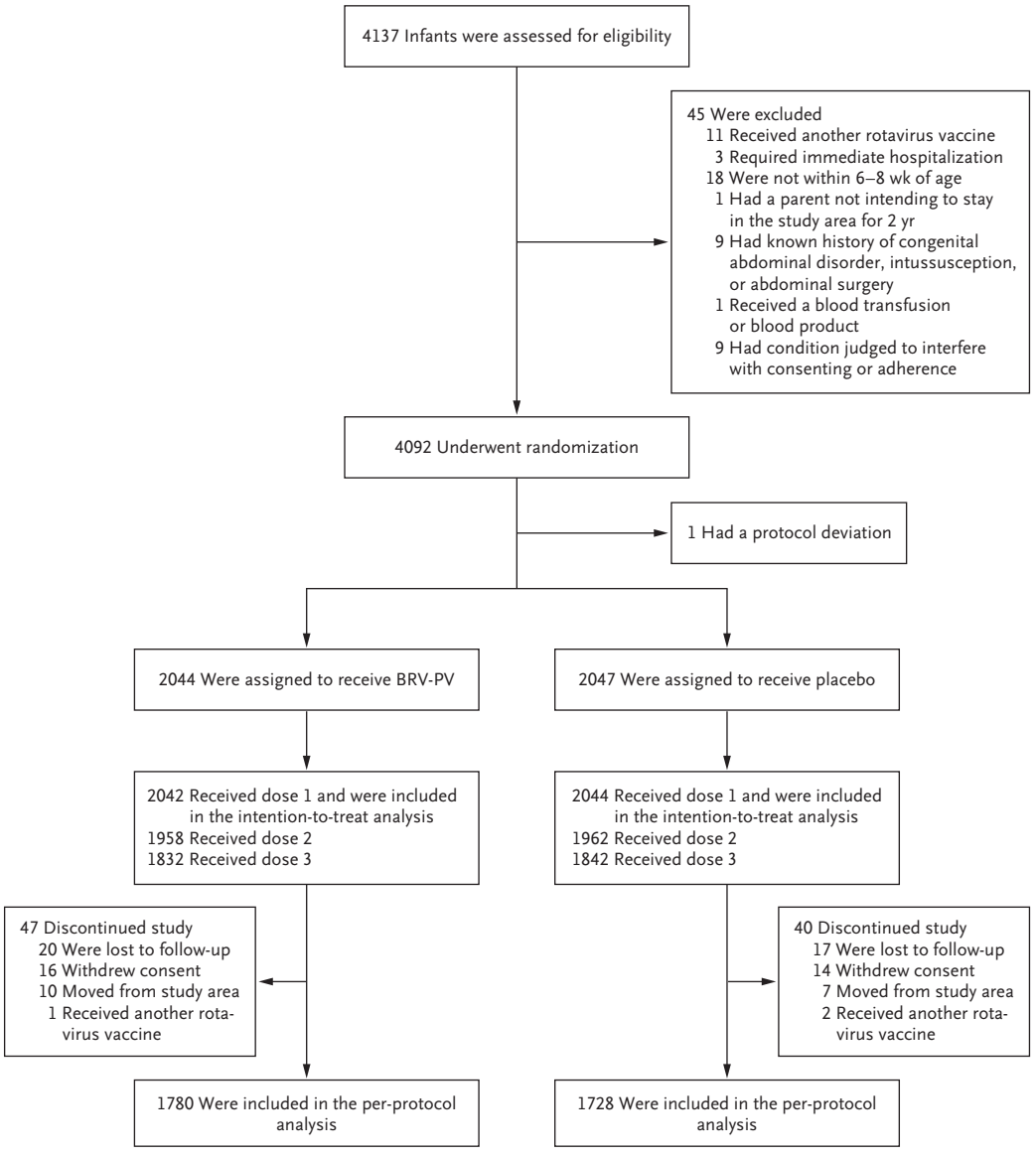

Figure 1. Enrollment and Outcomes.

Participants could have more than one reason for exclusion from the study. Included in the per-protocol analysis were infants who had received all three doses of vaccine or placebo according to the protocol and in whom no laboratory-confirmed episode of rotavirus gastroenteritis had occurred between the time of the first dose until 28 days after the third dose.

cebo group) were included in the per-protocol analysis. The characteristics of the infants in the two groups were similar at baseline (Table 1).

VACCINE EFFICACY

At 28 days after the third dose of vaccine or placebo, severe rotavirus gastroenteritis had been reported in 31 infants in the vaccine group and in 87 in the placebo group (2.14 cases vs. 6.44 cases per 100 person-years), resulting in a per-protocol vaccine efficacy of 66.7% (95% confidence interval [CI], 49.9 to 77.9) (Table 2). Vaccination with rotavirus vaccine prevented 4.30 (95% CI, 2.75 to 5.85) episodes of severe rotavirus gas-

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	BRV-PV (N=2044)	Placebo (N=2047)
Age — wk		
At dose 1	6.8±0.7	6.8±0.7
At dose 2	10.8±0.8	10.9±0.9
At dose 3	15.0±1.6	14.9±1.3
At end of efficacy follow-up	39.4±16.2	39.3±16.0
Male sex — no. (%)	1030 (50.4)	1004 (49.0)
Weight — kg	4.5±0.7	4.5±0.7
Length — cm	54.3±2.6	54.4±2.5
Coadministered with oral polio vaccine — no. (%)		
At dose 1	872 (42.7)	861 (42.1)
At dose 2	956 (46.8)	977 (47.7)
At dose 3	966 (47.3)	945 (46.2)

* Plus–minus values are means ±SD. There were no significant differences between the groups.

troenteritis per 100 person-years. Among the infants who had received at least one dose of vaccine or placebo (intention-to-treat population), severe rotavirus gastroenteritis was reported in 35 infants in the vaccine group and in 125 in the placebo group, resulting in a vaccine efficacy of 69.1% (95% CI, 55.0 to 78.7).

In both the per-protocol and intention-to-treat populations, the proportions of infants who did not have an episode of severe rotavirus gastroenteritis were significantly higher in the vaccine group than in the placebo group throughout follow-up (P<0.001) (Fig. 2). Vaccine efficacy increased with increasing severity of rotavirus gastroenteritis, and the between-group difference was significant for very severe gastroenteritis of any cause. There was no significant between-group difference in vaccine efficacy according to coadministration of the oral polio vaccine (Table S3 in the Supplementary Appendix, available at NEJM.org).

Table 2. Rate of Gastroenteritis and Vaccine Efficacy.

Population and Type of Gastroenteritis	BRV-PV (N=1780)		Placebo (N=1728)		Difference in Rate (95% CI)*	Percent Vaccine Efficacy (95% CI)
	No. with ≥1 Episode	Rate per 100 Person-Yr	No. with ≥1 Episode	Rate per 100 Person-Yr		
Intention-to-treat population						
Rotavirus gastroenteritis						
All cases	165	7.76	271	11.59	3.83 (2.01 to 5.65)	33.0 (18.7 to 44.8)
Severe cases	35	1.56	125	5.05	3.49 (2.46 to 4.51)	69.1 (55.0 to 78.7)
Very severe cases	7	0.31	35	1.37	1.06 (0.55 to 1.56)	77.4 (49.0 to 89.9)
Gastroenteritis from any cause						
All cases	853	59.68	901	53.09	–6.59 (–11.89 to –1.29)	–12.4 (–2.4 to – 23.4)
Severe cases	236	11.52	316	13.74	2.23 (0.12 to 4.34)	16.2 (0.8 to 29.2)
Very severe cases	23	1.02	80	3.17	2.15 (1.34 to 2.96)	67.7 (48.7 to 79.7)
Per-protocol population						
Rotavirus gastroenteritis						
All cases	121	8.71	172	13.29	4.58 (2.06 to 7.10)	34.5 (17.3 to 48.1)
Severe cases	31	2.14	87	6.44	4.30 (2.75 to 5.85)	66.7 (49.9 to 77.9)
Very severe cases	6	0.41	27	1.93	1.52 (0.72 to 2.32)	78.8 (48.6 to 91.2)
Gastroenteritis from any cause						
All cases	666	69.76	646	69.36	–0.40 (–7.93 to 7.13)	–0.6 (–12.1 to 9.7)
Severe cases	214	16.45	229	18.42	1.97 (–1.28 to 5.22)	10.7 (–7.6 to 25.9)
Very severe cases	21	1.45	62	4.52	3.08 (1.79 to 4.36)	68.0 (47.5 to 80.5)

* The between-group difference in the rate of gastroenteritis was calculated as the rate in the placebo group minus the rate in the BRV-PV group, so positive values favor the BRV-PV group, and negative values favor the placebo group.

ADVERSE EVENTS

Immediate adverse events (all grade 1 or 2 fever or vomiting) were reported in 3 infants in the vaccine group and in 1 in the placebo group (P=0.37). During the period between the first dose of vaccine or placebo and 28 days after the third dose, at least one adverse event was recorded in 1405 infants (68.7%) in the vaccine group and in 1376 (67.2%) in the placebo group (Table S2 in the Supplementary Appendix). Analyses of the adverse events showed a similar frequency of all classes of events in the two groups (P>0.15).

Fewer serious adverse events were reported in the vaccine group than in the placebo group (169 vs. 186 infants with ≥1 event, P=0.37) (Table 3). Overall, there was no significant difference in mortality between the vaccine group and the placebo group (27 deaths and 22 deaths, respectively; P=0.48). The most common causes of death were infections and infestations (in 37 infants) and metabolism and nutrition disorders (in 6) (Table S1 in the Supplementary Appendix). Medical investigators determined that no serious adverse event was related to the trial intervention. There were no confirmed cases of intussusception.

DISCUSSION

In this phase 3 trial in Niger, we found that three doses of BRV-PV, an oral rotavirus vaccine, protected healthy infants from severe rotavirus gastroenteritis. In a previous double-blind, placebo-controlled trial in Ghana, Kenya, and Mali, the efficacy of the RotaTeq vaccine against severe rotavirus gastroenteritis was 39.3% (95% CI, 19.1 to 54.7).[4] In a similar trial in South Africa and Malawi, the efficacy of the Rotarix vaccine was 61.2% (95% CI, 44.0 to 73.2).[7] In our trial, against a higher background incidence of severe disease than in the countries in the other two trials and with a vaccine efficacy of 66.7%, there were 4.30 fewer cases of severe rotavirus gastroenteritis per 100 infant-years among infants who received BRV-PV than among those who received placebo.

Efficacy estimates were lower than those observed in trials of other rotavirus vaccines among children in Europe and Latin America (80.5 to 90.4%),[10,12,28,29] a finding that is consistent with the results of studies comparing the efficacy of various vaccines against other diseases in these regions.[30-33] The same efficacy gradient has also been found in industrialized countries in analyses of differences according to socioeconomic status.[34] The underlying mechanisms for this finding remain poorly understood. Considerations have included the epidemiologic features of rotavirus infection (e.g., an earlier age at first infection among children in Africa, which confers natural protection in the placebo group),[35] host characteristics (e.g., poor nutritional status and differences in the gut microbiome, enteropathy, and enteric coinfections), and interference from maternal

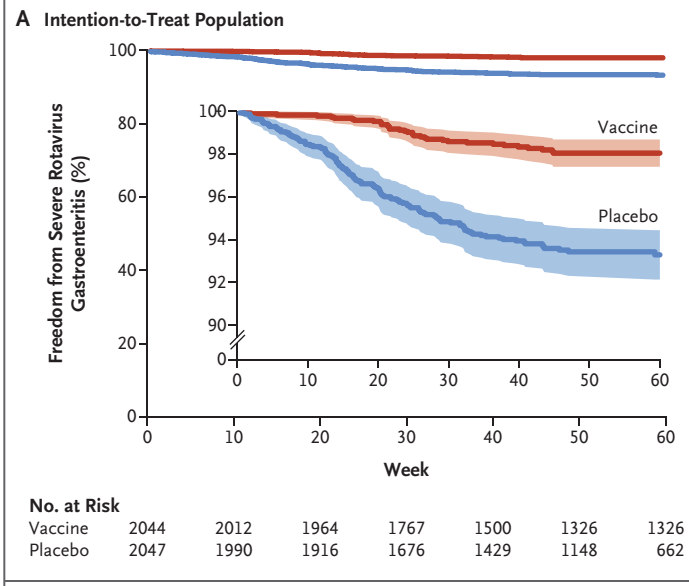

Figure 2. Freedom from Severe Rotavirus Gastroenteritis in the Two Trial Populations.

The inset in each panel shows the same data on an expanded y axis. The shaded areas indicate 95% confidence intervals.

Table 3. Serious Adverse Events.*

Event	BRV-PV (N=2044)	Placebo (N=2047)	P Value
At least one serious adverse event	169	186	0.37
At least one hospitalization	149	175	0.15
Blood or lymphatic system disorder	28	66	<0.001
Congenital familial or genetic disorder	6	13	0.17
Endocrine disorder	1	2	1.00
Gastrointestinal disorder	1	3	0.62
Infection or infestation	140	166	0.14
Injury or poisoning	8	8	1.00
Metabolism or nutrition disorder	52	57	0.70
Renal or urinary disorder	1	3	0.62
Skin or subcutaneous-tissue disorder	1	1	1.00
Vascular disorder	0	1	1.00
Death	27	22	0.48
Confirmed intussusception	0	0	NA

* All serious adverse events were coded according to the system organ class of the *Medical Dictionary for Regulatory Activities*, version 15.0, to standardize reporting. NA denotes not applicable.

antibodies in breast milk[36] and from coadministration of the oral polio vaccine, which can reduce rotavirus antibody levels.[37-39] Thus, there is a need to explore the role of prenatal nutritional status on immunogenicity and vaccine efficacy.

We did not identify any safety concerns with BRV-PV. Fewer serious adverse events and hospitalizations were reported among vaccinated infants than among those who received placebo. There was no significant difference in overall mortality between the groups and no plausible temporal or biologic causality for reported adverse events. No confirmed cases of intussusception were observed, a finding that was consistent with the results of other trials of oral rotavirus vaccine in the region.[40] However, this study was not powered to detect an increased incidence of rare events such as intussusception.

In 2013, the WHO recommended that rotavirus vaccine be administered whenever children present for routine immunizations, a protocol that would allow for relaxation of upper age restrictions and thus greater coverage.[2] In our trial, the vaccine efficacy in the intention-to-treat population (73.0%), in which the vaccine administration schedule was more flexible than that in the per-protocol population, may more closely represent the efficacy under real-world conditions. The use of a reduced two-dose schedule with pentavalent vaccines has advantages with respect to cost and logistics, but evidence has been consistent with respect to the higher efficacy of a three-dose schedule.[41]

This study has several important limitations. First, the vaccine was not consistently given concomitantly with the oral polio vaccine. However, secondary analyses that estimated vaccine efficacy according to whether BRV-PV was coadministered with oral polio vaccine suggested that the observed efficacy was not due to lower rates of concomitant administration. Second, the Vesikari score was originally designed for use in settings of high parental literacy,[25] which may have led to underscoring of some cases in our trial because of low parental literacy, although in such cases the results would not have differed between the two groups. Finally, at the time of the analysis, no extensive genotyping data were available to weigh the vaccine efficacy against a changing pattern of circulating serotypes, and the limited time period for this analysis precluded the inclusion of efficacy data up to 2 years of follow-up.

At present, 33 countries in sub-Saharan Africa either are using or plan to introduce rotavirus vaccines.[42] BRV-PV does not require refrigeration and has reasonable efficacy with respect to mor-

bidity and mortality from this preventable disease. Although no adverse-event signal was seen, large-scale surveillance will be needed to establish safety.

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